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1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/663,620	Short, J. M.
Examiner	**Art Unit**
Nashaat T. Nashed	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 22, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-166* is/are pending in the application.

4a) Of the above, claim(s) *31, 33-40, 52, 54, 56, 59-62, 88, 90-97, 112-115, and 118* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117, and 119-166* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

The application has been amended as requested in the communications filed January 17 and 29, 2002. Accordingly, claims 63-166 have been entered.

Applicant's election with traverse of Group I, claims 1-13, 17-21, 27-29 and 58 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the invention have the same classification and thus, searching the entire restricted inventions together does not represent a burden on the examiner. Applicants' argument have been found partially persuasive with regard to Groups I-IV and VI, claims 1-51, 53, 55, 57 and 58. The argument regarding Groups V and VII are not found persuasive because the various methods are distinct from one another having different steps and utilizing different methods, materials and in many instant have different products. Thus, they would require separate searches in the patent and non-patent literature.

Also, applicants' elected with traverse the "shuffling" as the method of mutation, and glycosidase as the enzymatic activity. Applicants traversal on the ground(s) that a search for on species would produce the prior art for all species. Applicants arguments have been fully considered by they are found unpersuasive. Each of the mutation methods and enzymatic activity has to be searched in the patent and non-patent literature, and thus, searching all the species together is burden some on the examiner. Applicant has provided no evidence on the record that suggests that the various species are obvious variants from one another. The restriction remains proper and therefore made **Final**.

Since claims 63-166 have been filed after the mailing of the restriction requirement on December 12, 2001, they were not included in the original restriction requirement. Claims belong to elected Group I are 1-51, 53, 55, 57, 58, 63-111, and 116-166. Claims 52, 54, 56, 59-62 and 112-115 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions, the requirement having been traversed above. Since the elected species for mutation and enzymatic activities are shuffling and glycosidase, claims 31, 33-40, 88, 90-97 and 118 are withdrawn from further consideration until a generic claim is found allowable.

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117, and 119-166 are under consideration in this Office action.

The disclosure is objected to because of the following informalities:

(i) Page 90, line 20, "a mini-ultracentrifuged 45k rpm at 20 degree for four hours" is not adequate description of centrifugation experiment. In order for the above description to be adequate, either the rotor of the centrifuge or the Gravitational force (G-force) should be identified. In the absence of the description of the rotor or the G-force, one of

ordinary skill in the art would not be able to reproduce the experiment described.

(2) Example 2 does not make any sense, in particular the first paragraph.

(3) The primers used in the PCR experiment on page 96, line 14 are not described or identified by a sequence identification numbers.

Appropriate correction is required.

The use of the trademark names have been noted in this application, see for example "OptiSeal" on page 92, line 23; Dinatech, page 93, line 24. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: "at least 1 kb in size" in claim 121, "at least 5 kb in size" in claim 122, "at least 10 kb in size" in claim 123, "at least 15 kb in size" in claim 124, "at least 20 kb in size" in claim 125, "at least 25 kb in size" in claim 126, "at least 30 kb in size" in claim 127, "at least 40 kb in size" in claim 128, "at least 60 kb in size" in claim 129, and "at least 200 kb in size" in claim 131.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 7 and 69 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claim 7 and 69 are different chemical compound and do not share a common structural feature required for the stated utility.

Claim 16 and 76 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claim 16 and 76 are different enzymatic activities and therefor do not share a common utility and a structural feature required for the stated utility.

Claim 21, 82, 156, and 165 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claim 21, 82 156, and 165 are various kind of organisms and do not share a common structural feature which is required for the stated utility.

Claim 30, 87, 146, and 158 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claims 30, 87, 146 and 158 are independent methods of mutating nucleic acid sequences and as such each of the method having different steps and provide different product(s).

Claims 79, 139, and 140 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claims 139 and 140 are various source and geographical location and do not share a common function or a structural feature required for the function.

Claims 135 is objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claims 135 are different chemical entities having no common utility or a structure feature required for such a utility.

Claim 138 is objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The various members of the Markush group in claim 138 do not share a common a structural feature required for the stated function.

Claim 48 is objected to because it contains non-elected subject matter.

Claims 53, 55, and 57 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 109, 110, and 116 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 63. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 12, 119, and 137 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 12, 119 and 137 do not further limit the claims from which they depend.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 63, 109, 110, 116, 119-125, 127, 129, 131, 132, 136-138 and 141-142 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 41-49, 52, 55, 56, 60, 62, 63, 68, and 69 of copending Application No. 09/375,605. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117, and 119-166 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,939,250 (250) in view of the prior art as exemplified by Stemmer *et al.* (see IDS, reference AE, U. S. Patent 5,605,793).

Claims 1-12 of the 250 patent are drawn to a process of identifying enzymatic activity comprising screening a library containing a plurality of clones containing DNA isolated from heterologous population of microorganisms for a specific activity; isolating a clone which is positive foe desired activity; subjecting said DNA in the clone to mutagenesis, and comparing the catalytic activity of the enzyme encoded by the mutated DNA to that of the wild-type.

Stemmer *et al.* teach a method of identifying proteins having desired activity using nucleic acid shuffling mutation method, constructing a library and screening the library for desired activity, see Figure 1, and column 4, lines 49-60, from line 60, column 8 through line 24, column 9.

Since there is constant need for identifying enzymatic activities with specific characteristics, one of ordinary skill in the art would have been motivated to use the mutation method described by Stemmer *et al.* in the method claimed in 250 patent. Thus, the claimed invention, as a whole, clearly *prima facie* obvious over the 250 patent.

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117, and 119-166 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,958,672 (672') in view of the prior art as exemplified by Arnold *et al.* (see IDS, reference AH, U. S. Patent 5,316,935) and Stemmer *et al.* (see IDS, reference AE, U. S. Patent 5,605,793).

Arnold *et al.* teach random mutagenesis to obtain modified subtilisin enzymes by the production of mutant genes, their expression in transformed host cells and screening to identify enzymes with desired activities (see column 7, lines 40-59).

The teaching of Stemmer *et al.* are summarized above.

Since one of the ordinary skill in the art would have had the motivation to identify new and improved enzymatic activity at the time of invention, it would have been obvious to the ordinary skilled artisan practicing claims 1-15 in 672' to obtain new bioactivities to further random mutagenesis of the gene encoding the desired activity and screen for desired characteristic such as improved thermal stability, enhances activity, or improved substrate specificity by mutagensis of a clone producing a desired biological activity by the method taught by Arnold *et al* or Stemmer *et al.*

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 62-87, 89, 98-108, 111, 117, 126, 128, 130, 133-135, 140, and 143-166 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-70 of U.S. patent application No. 09/375,605 (605) in view of the prior art as exemplified by Arnold *et al.* (see IDS, reference AH, U. S. Patent 5,316,935) and Stemmer *et al.* (see IDS, reference AE, U. S. Patent 5,605,793).

The teaching of Arnold *et al.* and Stemmer *et al.* are summarized above.

Since one of the ordinary skill in the art would have had the motivation to identify new and improved enzymatic activity at the time of invention, it would have been obvious to the ordinary skilled artisan practicing the invention of claims 41-70 of 605 application to obtain new bioactivities to further random mutagensis of the gene encoding the desired activity and screen for desired characteristic such as improved thermal stability, enhances activity, or improved substrate specificity by mutagensis of a clone producing a desired biological activity by the method taught by Arnold *et al* or Stemmer *et al.*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117, and 119-166 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases “bioactivity or biomolecule” in claims 1, 53, 55, 57, 58, 63, 109-111, and 116 "from a mixed population of cells" in claim 1, and 63 render the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes the phrase is taken to mean any chemical entity that can be detected.

(b) Claims 1, 53, 55, 57, 58, 63, 109, 110, and 116 are to incoplete methods for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (i) need a step of isolating the DNA of interest before the mutagenesis step; and (ii) screening step for bioactivity following the variegating step.

(c) Step (c) in claim 1 render the claims indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Step (c) is a comparison step between a wild-type bioactivity and that of mutagenized bioactivity. The effect is presumably is examined in a missing step which is screening for a desired bioactivity following the variegation step. So if the desired activity is an enhanced glycosidase activity relative to the wild-type activity, the variegated library will be screened for colonies having enhanced glycosidase activity relative to the wild type.

(d) The phrases “oligonucleotide comprising a detectable molecule” in claim 4, “labeled with fluorescent molecule” in claim 9, “oligonucleotide substantially ..... and having a detectable molecule” in claims 11 and 77, “oligonucleotide probe comprising detectable molecule” in claims 58 and 66, and “labeled with fluorescent molecule” in claim 71 render the claims indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. In the science of Chemistry, a molecule is defined as a single chemical entity. Thus, it is not possible to have an oligonucleotide (a molecule) comprising another detectable molecule. For examination purposes the phrase is taken to mean “an oligonucleotide comprising a detectable moiety”.

(e) the phrase “optical fluorescence” in claims 6 and 68 renders the claims indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. One of ordinary skill would not know any other kind of florescence and the specification does not teach any other kind. For examination purposes only, the word optical is not red in the claim.

(f) The phrases “or analogue thereof” in claims 7, and 69, “bioactive substrate” in claims 23, 48 and 105, and “substrate comprises C12FDG” in claim 24 render the claims indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

For examination purposes, it is assumed that the phrase"bioactive substrate", and "substrate comprises C12FDG" are interpreted to mean enzyme substrate and comprises fluorescence label, respectively. The phrase "or analogue thereof" is not red to the claim because no reasonable meaning could be given to the phrase.

(g) The clouse "wherein modulation of the interaction of the first test protein liked to the DNA binding moiety with the second test protein linked to the transcription activation moiety results in a change ...." in claim 25 renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. It is not clear to this examiner what is the first and the second test peptides are doing there and how the DNA binding moiety will affect the transcription. No reasonable meaning to the claim could be deduced.

(h) Claim 27 recites the limitation "The method of claim 1, further comprising, prior to step (d)", but claim 1 does not have step (d). Thus, there is insufficient antecedent basis for this limitation in the claim.

(i) Claim 41 recites the limitation "The method of claim 1, comprising screening the clone of (c) for", but step (c) of claim 1 is a comparison step. Thus, there is insufficient antecedent basis for this limitation in the claim.

(j) The phrase "chromogenic or fluorescent substrate" in the context of claim 66 render the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The word substrate is used in the application as enzyme substrate. For examination purposes only, the phrase is taken to mean "chromogenic or fluorogenic moiety.

(k) The clause "wherein the environmental sample is selected from ice, water, permafrost, material of volcanic origin, soil, and plants" in the context of claim 79 and 139 renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Surely, the applicant does not mean that. For examination purposes, the clause is taken to mean "wherein the environmental sample is obtained from ice, water, permafrost, a close proximity to volcanic vents, soil, and plants". Applicant should note the only material obtainable from volcanic origin are lava, minerals and rocks. No biological material is obtainable from volcanic origin.

(l) Claim 119 recites the limitation "The method of claim 116, further comprising the step of: expressing the mutagenized molecule of step (b)", but claim 116 does not have step (b); and the second step is mutagensis of the molecule. Thus, there is insufficient antecedent basis for this limitation in the claim, and the claim is confusing.

(m) Claim 137 recites the limitation "The method of claim 116, wherein the DNA molecules are inserted into a vector prior to step (a), but claim 116 does not have step (a); and the second step is mutagenizing the molecule. Thus, there is insufficient antecedent basis for this limitation in the claim and the claim is confusing.

(n) the word “fosmids” renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The application does not define the word fosmid and one of ordinary skill in the art would not know what is it. For examination purposes only, it is deleted.

(o) the phrase “improved activity” in claims 144, 148 and 166 renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase is not defined by the specification and one of ordinary skill in the art would not know in which way the activity to be improved. For examination purposes only, the phrase is taken to mean increased enzymatic activity.

(p) All other claims are included in this rejection because they are dependent on rejected claims and do not correct the deficiencies of the claim from which they depend.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8-24, 27, 28, 30, 41-48, 50, 51, 53, 55, 57, 58, 63-68, 70-87, 98-105, 107-111, 116, 117, 119-143 and 157-166 are rejected under 35 U.S.C. § 102(e) as being anticipated by Thompson *et al.* (U. S. P. 5,824,485).

Thompson *et al.* teach a method for screening molecular diversity by mixing and cloning genetic material from plurality of species of organism in a combinatorial gene library, see abstract and section 6, column 56 through 62. They teach that the genetic material can be obtained from any organism including those from environmental samples, plants and marine organisms to obtain antimicrobial, cancer or pharmaceutical compounds, see from column 12, line 35 through column 16, line 35. Also, they teach the preparation of the nucleic acid from donor organisms, see column 12, line 35 and section 5.3 starting in column 39, host cells see column 17, line 65, combinatorial expression libraries, see column 25, line 30, screening the combinatorial libraries, see column 32, line 58. Specifically, Thompson *et al.* teach the isolation of nucleic acid sequence from soil or other mixed environmental samples (uncultured), see section 5.3.6, column 41, protocol for the construction of prokaryotic

expression libraries and methods of screening the libraries, in particular for products of gene clusters such as secondary metabolites, see sections 5.4.1-5.4.14, columns 42-50, as well as methods for generating eukaryotic expression libraries using *E. coli*/*S. pombe* shuttle vector which would allow transferring the library from *E. coli* to *S. pmbe*, section 5.5, columns 50-55. In addition, Thompson *et al.* teach and claim forming a chimeric gene library (mutant gene library) from genes of interests to develop diversity of gene clusters such as those of polyketides (claims 1-3, 10-13, 14-21, 27, 28, 30, 41-47, 50, 51, 53, 55, 57, 58, 63-65, 74-82, 87, 107-111, 116-117, 119-143 and 157-166), see the entire document and, in particular, claims 1-45. The library can be constructed using <u>any host cell</u> such as the prokaryote *E. coli*, *Streptomyces* sp., or *Bacillus* sp., or the eukaryotic fungal cell such as yeast; uni- or a multicellular organisms (claims 99-104), , see section 5.1.3, starting on line 65, column 17. Section 5.2.2., column 36, starting on line 60, teaches of fluorescent or calorigenic (chromogenic) agents that can generate a detectable signal upon contact with desired bioactivity to be used for screening the library (claims 22-24, 66, 83, 84-86, and 105). Section 5.2.3., column 37, starting on lines 29, teaches the screening of the library with hybridization to molecular beacon DNA probe which encompasses fluorescence and chromogenic probes (claim 4-6, 11, 67, 68, and 70-73).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 5-7, 9, 13, 24, 26, 29, 32, 48, 49, 58, 66-71, 85, 86, 89, 106, and 144-156 are rejected under 35 U.S.C. § 103 as being unpatentable over Thompson *et al.* in view of the state of the art as exemplified by the cited art, Stemmer *et al.* (Stemmer *et al.* U. S. P. 5,811,238) and Arnold *et al.* (U. S. Patent 5,316,935) as well as all possible material available to one of ordinary skill in the art.

The teachings of Thompson *et al.* are summarized above.

Arnold *et al.* a method of obtaining mutants of subtilisin with desired characteristics which includes random mutagenesis of the gene encoding the enzyme by various method including PCR and site directed mutagenesis, incorporate the mutated now heterologous population of genes into expression vectors, transform suitable cell, and screen for a colony expressing subtilisin mutant with desired characteristics, see from line 19, column 7 through column 8, line 61, and example I-VIII.

Stemmer *et al.* teach a method of identifying proteins having desired and improved activity using nucleic acid shuffling mutation method, constructing a library and screening the library for desired activity, see Figure 1; and column 9, lines 30-48. Also, they teach the use of PCR primer, DNA fragments, DNA reassembly, and PCR error prone method to construct a library of mutants, see Figure 1 and examples 1-15.

Thompson *et al.* provide motivation for one of ordinary skill in the art to isolate a biological molecule of interest from an environmental sample and generate a library of Chimeric genes, and screen for desired biological product including nucleic acid encoding desired activity, protein, enzyme, polypeptides, and natural products such as polyketides. Also, Stemmer *et al.* provide one of ordinary skill in the art with a motivation to develop a method of identifying a protein with modified activity by generate a heterologous population of DNA from a gene encoding by mutagenesis, see column 4, lines 51-60. Thus, the ordinary skill in the art would have obtained an environmental sample, constructed a gene or cDNA library, normalize the library by well known methods in the art, screen for desired bioactivity, and isolate the DNA encoding the desired bioactivity as taught by Thompson *et al.*, subjected the gene or DNA to one of several random mutation methods taught by Stemmer *et al.* and Thompson *et al.*, construct an expression library comprising the heterologous DNA population, and screen for the desired improved activity by well known methods in the art including imobilizing a nucleic acid probe on solid support and that taught by Stemmer *et al.* (claims 29, 32, 89, and 106). Fluorescent hybridization methods are well known in the prior art which utilize a hybridization probe conjugated to well known fluorophore (a fluorescent moiety) such as umbelliferone, resorufin, fluorescein or rhodamine. One of ordinary skill in the art would be particularly motivated to use such a fluorophores because of their well known intense fluorescence spectrum (claims 5-7, 9, 58, 66-69 and 71). If the desired activity is an enzyme, it would have been obvious to one of ordinary skill in the art screen the library using a substrat including fluorescent substrates (claims 24, 48 and 85). Once a clone is identified

having the DNA encoding the desired activity, the DNA can be isolated by hybridization methods using a complementary sequence that could be attached to a solid support (claims 144-156). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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